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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/586,896	10/16/2006	Ferdinand Hermann Bahlmann	P/2107-297	4965

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EXAMINER	
DEBERRY, REGINA M	

ART UNIT	PAPER NUMBER
1647	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/586,896	BAHLMANN ET AL.	
	Examiner	Art Unit	
	Regina M. DeBerry	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *01 February 2010*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *4-6,10,15,19,32,39,40,45,49,52-54 and 57-64* is/are pending in the application.

4a) Of the above claim(s) *4-6,10,15,19,32,39,40,45,49,52,53 and 58-64* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *54 and 57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/2/09,2/1/10,3/31/10*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

Status of Application, Amendments and/or Claims

The amendment and Applicant's arguments, filed 01 February 2010, have been entered in full. Claims 4-6, 10, 15, 19, 32, 39, 40, 45, 49, 52, 53, 58-64 are withdrawn from consideration as being drawn to a non-elected invention. Claims 1-3, 7-9, 11-14, 16-18, 20-31, 33-38, 41-44, 46-48 50, 51, 55 and 56 are canceled. Claims 54 and 57 are under examination.

The Haller Declaration under 37 CFR 1.132 filed 01 February 2010 has been entered in full.

Information Disclosure Statement

The information disclosure statement(s) (IDS) (filed 12/2/09, 2/1/10 and 3/31/10) were received and comply with the provisions of 37 CFR §§1.97, 1.98 and MPEP § 609. They have been placed in the application file and the information referred to therein has been considered as to the merits. It is noted that lined references which state "considered do not print" have been considered by the Examiner, but will not be printed on the face of the patent issuing from this application because they are not true publications.

Withdrawn Objections And/Or Rejections

The rejection of claims 54-57 under 35 U.S.C. 112, second paragraph, as set forth at pages 3-4 of the previous Office Action (06 August 2009), is *withdrawn* in view of the amendment (01 February 2010).

The rejection to claims 54-57 under 35 U.S.C. 112, first paragraph, written description, new matter, as set forth at pages 4-6 of the previous Office Action (06 August 2009), is *withdrawn* in view of the amendment and Applicant's arguments (01 February 2010).

The rejection to claims 54-57 under 35 U.S.C. 112, first paragraph, enablement, as set forth at pages 6-9 of the previous Office Action (06 August 2009), is *withdrawn* in view of the amendment (01 February 2010). Please see the Scope of Enablement rejection below.

Claim Rejections-35 USC § 112, First Paragraph, Scope of Enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54 and 57 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for:

A method for treating acute or chronic renal failure in a human or animal patient exhibiting a) at least one dysfunction of endothelial cells, b) **hypertension** and c) at least one end-organ damage, wherein the at least one end-organ damage is selected from the group consisting of **left ventricular hypertrophy, microalbuminuria, proteinuria and glomerular filtration rate of 30 to 80 ml/min,** said method comprising administering to said patient a pharmaceutical composition comprising a subpolycythemia dosage of from 1 to 90 IU/kg of body weight per week of

erythropoietin or Aranesp, wherein the acute or chronic renal failure is thereby treated in said human or animal patient,

does not reasonably provide enablement for:

A method for treating acute or chronic renal failure in a human or animal patient exhibiting a) at least one dysfunction of endothelial cells and b) at least one cardiovascular risk, wherein the at least one cardiovascular risk is selected from the group consisting of **hypercholesterolemia, elevated asymmetric dimethylarginine (ADMA) levels, increased insulin resistance and hyperhomocysteinemia** and c) at least one end-organ damage, wherein the at least one end-organ is selected from the group consisting of **cognitive dysfunction and increased thickness of the intima media in the carotid artery**, said method comprising administering to said patient a pharmaceutical composition comprising a subpolycythemia dosage of from 1 to 90 IU/kg of body weight per week of **at least one of erythropoietin and a derivative thereof,** wherein the acute or chronic renal failure is thereby treated in said human or animal patient.

The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicant argues that the data presented in the application is sufficient to enable the claimed method involving treatment of a specific group of patients, i.e. those suffering from acute or chronic renal failure, which are exhibiting hypertensive damage and end-organ damage caused thereby. Applicant states that Examples 3 and 4 of the

specification demonstrate that EPO treatment has a positive effect on the kidney tissue of animals exhibiting renal insufficiency. Applicant argues that Figures 11-14 demonstrate the histological changes in the Sprague-Dawly rats exhibiting chronic renal failure associated with severe end-organ damage causing a reduced glomerular filtration rate and hypertension (cardiovascular rate risk). Applicant argues that Figure 6 indicates that patients with restricted renal function exhibit a distinct endothelial progenitor cell dysfunction and the rats represent the specific patient population. Applicant discusses Bahlmann et al. (newly submitted reference; Low-dose therapy with long-acting erythropoietin analogue Darbepoietin alpha persistently activates endothelial Akt and attenuates progressive organ failure", Circulation Aug 9, 2004, pgs 10006-1012). Applicant argues that the reference is co-authored by Bahlmann, who is also one of the co-inventors of the instant application. Application discusses the Haller Declaration under 37 CFR 1.132.

Applicant's arguments have been fully considered and are found partly persuasive. As was stated in the previous Office Action, the Examples teach that EPO treats at least one dysfunction of endothelial cells (such as increasing endothelial proliferation) and reduces the progression of chronic and acute renal failure upon administering EPO in rat animal models. One skilled in the art could assume that renal failure would also encompass at least one dysfunction of endothelial progenitor cells. Further, Bahlmann et al. teach chronic renal disease progression in the established nephrectomy rat remnant kidney (RK) model. Bahlmann et al. teach that the animal model features progressive injury to the renal microvascular endothelium leading to

glomerular sclerosis accompanied by ischemia-induced tubulointerstitial damage (page 1007, 1st paragraph). The reference teaches increased urinary protein excretion in saline-treated RK rats compared to Darbepoietin-treated RK rats. The reference teaches increased systolic blood pressure in saline-treated RK rats compared to Darbepoietin-treated RK rats. Glomerular sclerosis and tubulointerstitial damage was reduced in Darbepoietin-treated RK rats (page 1007, last paragraph and page 1008). Thus one skilled in the art could assume that renal failure would also encompass symptoms such as hypertension, left ventricular hypertrophy, microalbuminuria, proteinuria and glomerular filtration rate of 30 to 80 ml/min.

However, the claims as recited are not enabled. The specification pointed out by Applicant (Examples 3 and 4 and Figures 11-14) and the submitted reference fail to demonstrate enablement for treating chronic or acute renal failure patient in a human or animal patient with EPO, wherein said patient exhibits at least one dysfunction of endothelial progenitor cells ***AND*** at least one cardiovascular risk, wherein the at least one cardiovascular risk is selected from the group consisting of *hypercholesterolemia, elevated asymmetric dimethylarginine (ADMA) levels, increased insulin resistance* and *hyperhomocysteinemia* ***AND*** at least one end-organ damage, wherein the at least one end-organ damage is selected from the group consisting of *cognitive dysfunction and increased thickness of the intima media in the carotid artery.* Bahlmann et al. teach that the RK animal model is made by ligating the left renal artery. Bahlmann et al. teach various symptoms in this animal model. The specification and the references of record fail to teach, for example, symptoms such as cognitive dysfunction ***AND*** increased

insulin resistance would be aspects in chronic or acute renal failure in human or animals.

The Haller Declaration under 37 CFR 1.132 is insufficient to overcome the rejection as set forth in the last Office action. The submitted data (Attachment A and Attachment B) appear to **employ 2 *different* patient populations**; one suffering from acute or chronic renal failure exhibiting a reduced number of endothelial cells (i.e. dysfunction of endothelial cells), high blood pressure (i.e. hypertension) and a patient population suffering from type II diabetes exhibiting a reduced number of endothelial cells and hypertonia. Administered EPO increased the number of endothelial cells. However, the patient populations do not fall within the scope of the claims as recited. The instant claims are drawn to treating chronic or acute renal failure. The Haller Declaration fails to demonstrate enablement for *treating chronic or acute renal failure* in a human or animal patient with EPO, wherein said patient exhibits at least one dysfunction of endothelial progenitor cells ***AND*** at least one cardiovascular risk, wherein the at least one cardiovascular risk is selected from the group consisting of hypercholesterolemia, elevated asymmetric dimethylarginine (ADMA) levels, increased insulin resistance and hyperhomocysteinemia ***AND*** at least one end-organ damage, wherein the at least one end-organ damage is cognitive dysfunction and increased thickness of the intima media in the carotid artery.

Applicant concludes by stating that the specification (pages 21-22) describes the term "derivative" and that it is believed to be clear that one having an ordinary level of skill in the relevant art would be well qualified to decide which material(s) are, and are

not, derivatives of EPO. Applicant argues that they respectfully traverse the Examiner's statement at page 8 of the Office Action to the effect that the instant examples employ EPO, not derivatives thereof. Applicant argues that instant Examples 3 and 4 in the specification disclose the use of an EPO derivative, namely Aranesp, which was also described in the paper by Bahlmann et al.

Applicant's arguments have been fully considered but are not found persuasive. Page 23 of the specification states, "the differences between an erythropoietin derivative and native erythropoietin may arise, for example, through mutations such as deletions, substitutions, insertions, additions, base exchanges and/or recombinations of the nucleotide sequences coding the erythropoietin amino acid sequences" (page 23). Page 22 of the specification states, "according to the invention, the term derivative also includes fusion proteins, in which functional domains of another protein are present on the N-terminal part or on the C-terminal part". As was stated in the previous Office Action, the specification would not support claims to EPO polypeptides modified to an unlimited extent relative to those exemplified. The disclosure provides no guidance as to which regions of the proteins would be tolerant of modification and which would not. The artisan would accordingly have no resort save trial-and-error experimentation to determine which of the astronomically large number of possible structural variants had the functional properties of the claimed proteins. Such experimentation would be undue for one skilled in this art. The scientific reasoning and evidence as a whole indicates that the rejection should be maintained.

NEW CLAIM REJECTIONS

Claim Rejections-35 USC § 112, First Paragraph, Written Description (New Matter)

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 54 and 57 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. **This is a new matter rejection.**

The specification as originally filed does not provide support for the invention as now claimed:

"..**increased** insulin resistance.." (claim 54)

Applicant's amendment, filed 29 April 2009, asserts that no new matter has been added and directs support to claims 38-40, 44-45 and claims 9, 55 and 56. The wording is not apparent from said sections.

The Examiner has found the limitations:

"..insulin resistance.." (pages 6, 7, 13, 17, 20, 28, 35, 36, 43, 50 and 63). The Examiner cannot find increased insulin resistance.

The specification as filed does not provide a written description or set forth the metes and bounds of these "limitations". The instant claims now recite limitations which

were not clearly disclosed in the specification as filed, and now change the scope of the instant disclosure as-filed.

Applicant is required to cancel the new matter in the response to this Office action. Alternatively, Applicant is invited to provide *specific written support* for the "limitations" indicated above or rely upon the limitations set forth in the specification as filed.

Claim Rejections-35 USC § 103(a)

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 54 and 57 are rejected under 35 U.S.C. 103(a) as being unpatentable over Jungers et al., Nephrology Dialysis Transplantation 16:307-312 (2001) in view of

Stehouwer et al., Nederlands tijdschrift voor geneeskunde. Abstract in English. Vol. 141/No. 34:1649-53 (Aug 23 1997).

The instant claims are drawn to a method for treating acute or chronic renal failure in a human or animal patient exhibiting a) at least one dysfunction of endothelial progenitor cells, b) at least one cardiovascular risk factor, wherein the at least one cardiovascular risk factor is selected from the group consisting of hypertension, hypercholesterolemia, elevated asymmetric dimethylarginine (ADMA) levels, increased insulin resistance and hyperhomocysteinemia and c) at least one end-organ damage, wherein the at least one end-organ damage is selected from the group consisting of left ventricular hypertrophy, microalbuminuria, cognitive dysfunction, increased thickness of the intima media in the carotid artery, proteinuria and a glomerular filtration rate of 30 to 80 ml/min, said method comprising administering to said patient a pharmaceutical composition comprising a subpolycythemic dosage of from 1 to 90 IU/kg of body weight per week of at least one of erythropoietin and a derivative thereof, wherein the acute or chronic renal failure is thereby treated in said human or animal patient.

Jungers et al. teach that the effects of rHuEPO therapy on blood pressure and the rate of progression of chronic renal failure (CRF) are still disputed. Jungers et al. teach that 20 CRF patients received 54.3+_ 16.5 U/kg/week of EPO (abstract and page 308, Results column, 2nd paragraph)**(applies to claim 54 and 57**). Jungers et al. teach the treatment of hypertension and the progression of CRF in CRF patients. Jungers et al. teach that in clinical studies, using lower doses of rHuEPO, thus achieving a more progressive correction of anemia; elevation of blood pressure was no longer observed

and no acceleration of the progression of renal disease was noted. Jungers et al. teach that recently it has been claimed that correction of anemia with Epoetin may instead reduce the progression of renal failure in predialysis patients. Jungers et al. teach that their data provides conclusive evidence that EPO therapy was associated with a substantial extension of renal autonomy in EPO treated patients, when compared to untreated patients with a similar degree of renal failure. Jungers et al. teach that a slowing of progression was observed in EPO treated patients. Jungers et al. teach that EPO therapy has been shown to partially protect against the development of left ventricular hypertrophy (Abstract and Discussion page 309, last paragraph). Jungers et al. teach that hypoxia stimulates the development of interstitial fibrosis and that EPO seems to alter tissue hypoxia. Partial correction of hypoxia may be expected to reduce the development of interstitial fibrosis, which has been shown to be a major factor of the progression of renal disease. Jungers et al. teach that EPO results in substantial delay in the need for renal replacement therapy (page 311, 7th full paragraph and last paragraph).

Stehouwer et al. teach that microalbuminuria, hypertension, endothelial dysfunction and an increased risk of left ventricular hypertrophy are aspects in CRF patients.

It would have been obvious at the time the invention was made to modify a method of treating CRF patients comprising administering 54.3+_ 16.5 U/kg/week of EPO to CRF patients exhibiting hypertension, wherein CRF is treated as taught by Jungers et al. by administering 54.3+_ 16.5 U/kg/week of EPO to CRF patients

exhibiting microalbuminuria, hypertension, endothelial dysfunction and left ventricular hypertrophy with a reasonable expectation of success. The motivation and expected success is provided by Jungers et al. and Stehouwer et al. Jungers et al. teach that when using lower doses of rHuEPO, elevation of blood pressure was no longer observed and no acceleration of the progression of renal disease was noted. Jungers et al. teach that EPO therapy has been shown to partially protect against the development of left ventricular hypertrophy. Jungers et al. teach that hypoxia stimulates the development of interstitial fibrosis and that EPO seems to alter tissue hypoxia. Partial correction of hypoxia may be expected to reduce the development of interstitial fibrosis, which has been shown to be a major factor of the progression of renal disease. Stehouwer et al. teach that microalbuminuria, hypertension, endothelial dysfunction and an increased risk of left ventricular hypertrophy are aspects in CRF patients.

It would be obvious to administer EPO at lower doses (such as 54.3+_ 16.5 U/kg/week) to treat CRF in CRF patients exhibiting microalbuminuria, hypertension, endothelial dysfunction and left ventricular hypertrophy because Jungers et al. teach that no acceleration of the progression of renal disease was noted in CRF patients. Jungers et al. teach a slowing of progression in EPO CRF treated patients.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP

§ 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Regina M. DeBerry whose telephone number is (571) 272-0882. The examiner can normally be reached on 9:00 a.m.-6:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on (571) 272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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4/19/10